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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,996	10/17/2003	Lothar Steidler	2676-6096US	1934

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/687,996	STEIDLER, LOTHAR	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *11 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-17 and 21-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed September 11, 2006amending claims 1, 5 and 12 and adding claims 21-30 has been entered.

Claims 1-30 are pending. Claims 11 and 18-20 have been previously withdrawn

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

Applicant is advised that should claim 1 be found allowable, claim 22 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21 and 23-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 21, with dependent claims 24-26 and 30, is drawn to an isolated *Lactococcus* bacterium comprising a defective thymidylate synthase gene. Claims 23 and 27-29 depend from claim 21 and limit the *Lactococcus* bacterium to *Lactococcus lactis*. Therefore the claims recite the genus of *Lactococcus* bacterium comprising a defective thymidylate synthase gene, said *Lactococcus* bacterium comprising both naturally occurring defects in thymidylate synthase gene and defects caused by molecular biological techniques. Furthermore, the genus of *Lactococcus* species is diverse genus that encompassing thymidylate synthase gene or genes from any species of *Lactococcus*, including the subgenus of thymidylate synthase gene(s) from any subspecies of *L. lactis*.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants

must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification the genus of the genes of *Lactococcus* thymidylate synthase gene(s), including the subgenus of *L. lactis* thymidylate synthase gene(s), is represented by a single thymidylate synthase from *L. lactis* subsp. *lactis* that is disrupted by a functional human interleukin-10 expression cassette. The specification fails to describe any other representative species *Lactococcus* thymidylate synthase gene(s) by any identifying characteristics or properties other than the functionality of being *Lactococcus* thymidylate synthase gene(s).

The specification fails to define those structural features of *Lactococcus* thymidylate synthase gene(s) that are commonly possessed by members of the genus that distinguish them from others. The specification fails to provide the structure and function correlation common to all members of the genus of *Lactococcus* thymidylate synthase gene(s). Thus, one skilled in the art cannot visualize or recognize the identity of the members of the genus.

Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention

in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention at the time of filing.

Claims 21 and 23-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *Lactococcus* bacterium comprising a disrupted thymidylate synthase gene, said gene comprising SEQ ID NOs: 3 or 5, does not reasonably provide enablement for a *Lactococcus* bacterium comprising a disrupted thymidylate synthase gene having an undefined percent identity to SEQ ID NOs: 3 or 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification does not support the broad scope of the claim which encompasses comprising a disrupted thymidylate synthase gene from any *Lactococcus* bacterium having no known identity to SEQ ID NOs:3 or 5. The specification does not teach thymidylate synthase genes from other species of *Lactococcus* including other

subspecies of L. lactis. While recombinant hybridization techniques are known, only highly homologous sequences can be identified using a given nucleic acid sequence. The state of the art provides no reasonable expectation of success in obtaining nucleic acid encoding a thymidylate synthase gene having an unknown identity to SEQ ID NOs: 3 or 5 and the result of such screening is unpredictable.

Without sufficient guidance, beyond that provided, disruption of thymidylate synthase genes of an unknown structure is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 12-17 and 21-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5 and 12 recite "a defective thymidylate synthase gene, ... wherein said thymidylate synthase gene is selected from the group consisting of SEQ ID NO:3 and SEQ ID NO: 5" (emphasis added). The claims are confusing because "said gene" is a defective gene whereas SEQ ID NOs:3 and 5 are sequences of the endogenous non-defective genes.

Claim 21 is unclear. the claim recites a bacterium comprising a genome. Every bacterium comprises a genome. It further recites "a means for encoding a defective thymidylate synthase gene". The metes and bounds of "a means" are not defined in the specification and are not clear. Further, claim 21 recites "wherein said genome has been genetically modified in comparison to wild-type *Lactococcus*". It is unclear whether genome is modified due to modification in thymidylate synthase gene resulting in its inactivation or due to any other independent modification.

Claim 22 is confusing as reciting "wherein the means for encoding a defective thymidylate synthase gene comprises a thymidylate synthase gene selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5". It appears that defective and non-defective gene are encoded by the same sequence.

Claims not specifically discussed herein are rejected as dependent from the rejected base claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21 and 23-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steidler et al. in view of Taylor et al.

Steidler et al. (from PTO-1449 filed 10/17/03) teach a transformed *L. lactis* strain which secretes active murine interleukin-10 that is used to treat murine colitis.

Taylor et al. (from PTO-1449 filed 10/17/03) teach the disruption of the thymidylate synthase gene in *Saccharomyces cerevisiae* (see abstract and page 5302, right column, last paragraph to page 5303, left column, 1st paragraph). They teach that the disruption of said thymidylate synthase by inserting a 2.2 kb fragment of LEU2 gene. They further teach that such disruption results in dependence on dTMP for growth. They teach that thymidylate synthase genes from various organisms show similar properties t the functional level (page 5304, left column, 2nd paragraph- right column, 1st paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce a *L. lactis* strain which comprising a disrupted thymidylate synthase. This would allow to use said strain for the delivery of a drug (molecule of interest) to a patient without contaminating the outside environment where thymidine/thymine is not present in amount sufficient for said strain to survive. One of such molecules of interest can be interleukin-10, importance of which is taught by Steidler et al. One of ordinary skill in the art would have a reasonable expectation of success because the disruption of genes in bacteria were widely and routinely performed at the time the invention was made.

Response to Arguments

Applicant's arguments filed September 11, 2006 have been fully considered but they are not persuasive.

With regard to the 112, 1st paragraph written description and enablement rejections Applicant argues that that haven overcome in view of the amendment limiting the thymidylate synthase gene to SEQ ID NOs:3 or 5. this is agreed with. However, new claims 21 and 23-30 require these rejections.

With regard to the 112, 2nd paragraph rejection, the outstanding rejections not reiterated above are withdrawn in view of the amendment and Applicant's arguments.

With regard to the 103(a) rejection Applicant argues that "the combination of Steidler and Taylor does not teach each and every element of claims 1, 5, and 12 as amended. Specifically, claims 1, 5, and 12, as amended, direct "wherein said thymidylate synthase gene is selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5". Applicants respectfully assert that the combination of Steidler and Taylor does not teach that the thymidylate synthase gene is selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5" (Remarks, pages 9-10). This is agreed with and claims 1, 5 and 12 are no longer rejected under 103(a). However, claims 21 and 23-30 require said rejection. Applicants further argues that Steidler teaches away from the invention with reference to pages 5302-5303 (page 10). The examiner was not able to find said pages in the reference. Applicants further argues that "there is no reasonable expectation of success. Taylor describes the disruption of the TMP1 gene in the yeast *S. cerevisiae*, by homologous recombination. However, homologous

recombination is relatively frequent in this yeast, whereas it is rare in *Lactococcus*. Moreover, as genomic integration by homologous recombination is a rare event, even in yeast, a very efficient transformation system is needed. Therefore, although gene inactivation by homologous recombination is a standard technique in yeast, application in other organisms, especially in bacteria like *Lactococcus* sp., where the transformation efficiency is rather low, is far from evident" (pages 10-11). It is noted that the claims do not require homologous recombination, just defective genes. It is known that *thyA* mutants are isolated from bacteria, such as *Rhizobium meliloti*, for example (Ross et al. Appl. Environ. Microbiol.(July 1990) Vol. 56, No. 7, pages 2164-2169, form PTO-1449 filed 10/17/03).

Conclusion

The post filing art made of record and not relied upon is considered pertinent to applicant's disclosure.

Steidler et al "Biological containment of genetically modified *Lactococcus lactis* for intestinal delivery of human interleukin 10". Nature Biotechnology (July 2003) Vol. 21, No. 7, pages 785-789, describes the instant invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

January 18, 2007